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THE STEREOCHEMISTRY OF 20-*ISO*SAPOGENINS

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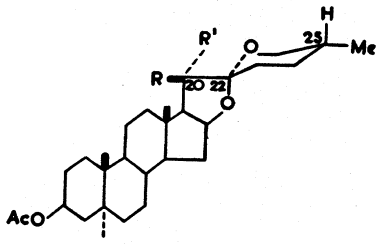
The stereochemistry of the spiroketal side chain of natural and 20-*iso*sapogenins (*cyclopseudo*sapogenins) has been in recent years the subject of a number of investigations in the United States and Great Britain.[1-3] There is now substantial agreement on the stereochemistry of the former group[1,3] but disagreement on the latter.[1,2] The 20-*iso*sapogenins are formed by the cyclization of *pseudo*sapogenins under dilute acidic conditions and two asymmetric centres, C(20) and C(22), may be involved. We now wish to report a partial synthesis of 20-*iso*tigogenin by a new route which in the crucial step involves only the C(20) asymmetric centre.

Oxidation of 20-*iso*tigogenin acetate[4] with chromic oxide in acetic acid gave a new sapogenin (I) with an additional hydroxyl group, [m.p. 238–240°; $[\alpha]_D^{25}$-71° (Found: C, 73·92; H, 10·24. $C_{29}H_{46}O_5$ requires C, 73·38; H, 9·77%)]. That the new hydroxyl function in compound (I) was tertiary was shown by its resistance to prolonged chromic oxide oxidation and acetylation in hot pyridine-acetic anhydride and by the infrared spectra showing a strong, bonded hydroxyl band (CS_2 solution) at 3510 cm.$^{-1}$. Dehydration of compound (I) with thionyl chloride in pyridine gave the unsaturated sapogenin (II) [m.p. 190–191°; $[\alpha]^{25}$–89·5°; $\lambda_{max.}$=211 mμ (ε=1220); spiroketal "fingerprint" bands[5,6] 984(s), 938(w), 923(m), 903(s), 897(s) and 863(w) cm.$^{-1}$, identical with tigogenin acetate[5] except for the 903 band (Found: C, 76·42; H, 9·98. $C_{29}H_{44}O_4$ requires C, 76·27; H, 9·71%)]. The close similarity of the infrared spectra of compound (II) and tigogenin acetate coupled with the fact that compound (II) is stable towards hot ethanolic hydrochloric acid strongly suggests that the substance (II) is identical at C(22) and C(25) with tigogenin and other 25D-natural sapogenins as shown in the accompanying formulae. The location of the double bond in substance (II) was established as follows: reaction of the compound with osmium tetroxide gave the diol-monoacetate (III) [m.p. 217–220°; $[\alpha]_D^{25}$–67°; $\nu_{max.}$ 3620, 3520 and 1736 cm.$^{-1}$ (Found: C, 71·25; H, 9·30. $C_{29}H_{46}O_6$ requires C, 70·98; H, 9·45%)] which on treatment with periodic acid gave formaldehyde and a sapogenin with a ketone in a five membered ring (IV), [m.p. 180–191°; $[\alpha]_D^{25}$–87°; $\nu_{max.}$ 1762 and 1735 cm.$^{-1}$ (Found: C, 73·04; H, 9·15. $C_{28}H_{42}O_5$ requires C, 73·32; H, 9·23%)]. Compound (IV) was also obtained by ozonization of compound (II). Analysis of the physical and chemical properties of compound (II) shows that this compound has a methylene group which must be attached to C(20), and which is responsible for the additional strong 903 cm.$^{-1}$ band.[7] Therefore (II) is formulated as 5α : 22a : 25D-spirost-20(21)-en-3β-ol 3-acetate. Molecular models show that the rear or α side of (II) is relatively unhindered at C(20) and C(21) whereas approach of entering groups from the β face would be severely restricted. By analogy to the classical "rule of the rear"[8] the diol (III) was formed by rear side attack of the osmium tetroxide so that (III) must be 5α : 20β : 22a : 25D-spirostane-3β : 20α : 21-triol 3-acetate and compound (IV) is formulated as 20-oxo-5α : 20-nor : 22a : 25D-spirostan-3β-ol 3-acetate.

Treatment of compound (III) with toluene-*p*-sulphonyl chloride gave the 21-tosylate (VI), characterized by infrared spectra but not isolated in pure form, which on reduction with lithium aluminum hydride and acetylation gave compound (I) which may thus be formulated as 5α : 20β : 22a : 25D-spirostane-3β : 20α-diol 3-acetate. Models of (I) indicate that in the compound as formulated there should be strong hydrogen bonding between the C(26) oxygen and the C(20α) hydroxyl which is *cis* to this oxygen atom. As described earlier, the infrared spectrum of compound (I) shows strong hydrogen bonding in the hydroxyl region.

Finally, catalytic hydrogenation of compound (II) with platinum oxide in neutral solvents gave 20-*iso*tigogenin acetate,[4] (VII). Again, the hydrogenation took place in accordance with the rule of rear side attack[8] since frontal attack would have necessarily given tigogenin acetate. Since the hydrogenation was carried out under neutral conditions which preclude any attack on the sapogenin side chain, compound (VII) must be formulated as 5α : 20β : 22a : 25D-spirostan-3β-ol 3-acetate in complete agreement with the formulation arrived at previously from a consideration of molecular rotation data.[1]



(I; R=Me, R'=OH)

(II; $\begin{matrix}R\\R'\end{matrix}>=\!=CH_2$)

(III; R=CH_2OH, R'=OH)

(IV; $\begin{matrix}R\\R'\end{matrix}>=\!=O$)

(V; R=CH_2—O—C(=O)—Me, R'=OH)

(VI; R=CH_2—$OSO_2C_6H_4Me$, R'=OH)

(VII; R=Me, R'=H)

FIG. 1.—*Steroidal Sapogenins . . . Stereochemistry of the Spiroketal Ring System.*

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